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Ethylene Oxide: Position Document 1

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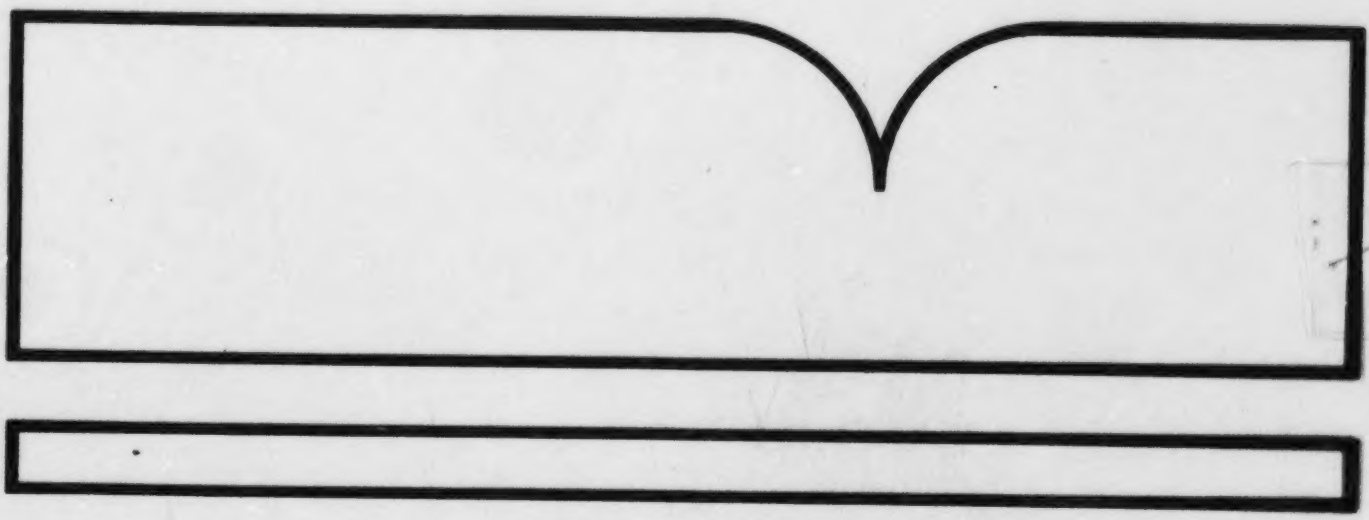

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Ethylene Oxide Working Group
J.B. Boyd, Project Manager
U.S. Environmental Protection Agency

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I. Background

A. Chemical and Physical Properties

Ethylene oxide (EtO), which is also known as oxirane, is a gas at room temperature and normal atmospheric pressure. It is the simplest epoxide or cyclic ether. EtO has a boiling point of 10.7°C and a molecular weight of 44.5, and is infinitely soluble, yet reactive, in water, alcohol, and ether. It is a highly reactive and penetrative alkylating agent with the following structural formula.

B. Environmental Chemistry Characteristics

Due to its high reactivity, EtO is unlikely to persist chemically unaltered. The half-life of EtO in water was reported to be 76 hours at 37°C and 6 months at 4°C (20). It reacts with water to produce ethylene glycol, with hydrogen halides to produce ethylene halohydrins, with alcohols and phenols to produce ethylene glycol ethers, with acids to produce ethylene glycol esters, with amines to

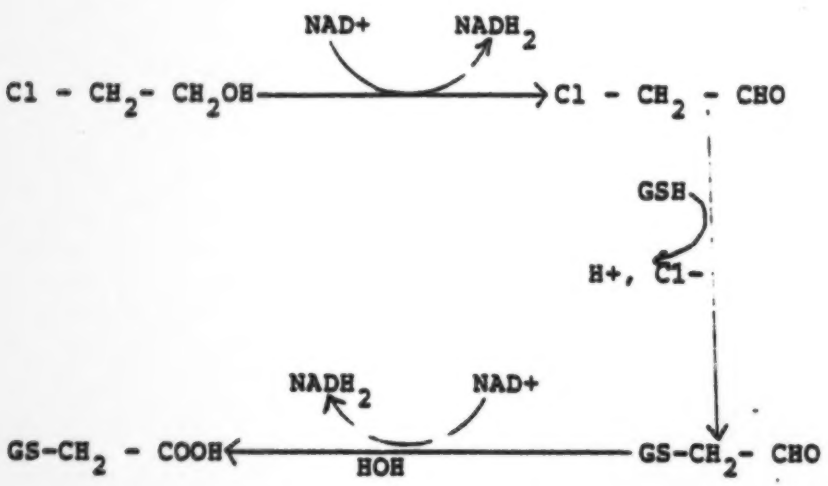
produce ethanolamines, and with sulphhydryl compounds to produce thioethers. The two most commonly found degradation products are ethylene chlorohydrin (ECH) and ethylene glycol (EG). After sterilization and fumigation of various organic materials and synthetic objects with EtO, residues of EtO, ECH, and EG are found. Foods (25,68,79,89), drugs (1,35), medical supplies (6,14,30,59,64), and medical devices (31,52) have been shown to contain one or more of these residues following treatment with EtO.

An in vitro study of mouse spleens incubated with tritium-labeled EtO demonstrated that EtO chemically binds with DNA and proteins, and that the biological half-life of EtO was approximately 9 minutes (20).

C. Metabolism

By monitoring cofactors and metabolites, Johnson (44) deduced that ^{36}Cl-labeled ECH was dehydrogenated when incubated with rat liver homogenate (supernatant following 60,000 x g for 1 hour). Besides the liberated ^{36}Cl ion, the only product observed to be generated in this in vitro procedure was S-carboxymethyl glutathione ($GS-CH_2-COOH$). The presence of the cofactor, nicotinamide-adenine dinucleotide (NAD+), in the homogenate was essential to the

observed metabolic activity. The reduced form of NAD+, which is represented as $NADH_2$, was generated during incubation. Following oral administration of unlabeled ECH (52 mg/kg or more), the rat glutathione (GSH) levels fell rapidly. $GS-CH_2-COOH$ was also identified in the rat liver extract within 45 minutes after a dose of 100 mg/kg was administered. This <u>in vivo</u> observation further suggests that $GS-CH_2-COOH$ is an intermediate in the metabolism of ECH. By including and excluding various metabolites, cofactors, competitive inhibitors, and substrates, the author proposed the following metabolic pathway.



Blair and Vallee (9) demonstrated the ability of purified human liver alcohol dehydrogenase to oxidize monochloroacetaldehyde and ECH.

Ehrenberg et al. (20) observed that five mice exposed by inhalation to tritium-labeled EtO excreted an average of 78% of the estimated dose within 48 hours. Only one of the excretory products was characterized. Two mice were exposed to 1.15 ppm EtO for 75 minutes; two were exposed to 7.4 ppm for 60 minutes; and one was exposed to 33 ppm for 75 minutes. There was a trace amount of 7-hydroxyethylguanine in the two mice exposed to 7.4 ppm. Ehrenberg also examined the organs of 15 mice after they were exposed to air containing 1.15 ppm ^{3}H-labeled EtO for 75 minutes. Radioactivity was found in the testes, kidneys, livers, and spleens.

D. Registered Uses

There are 38 Federally registered pesticide products containing EtO as an active ingredient. One Federally registered product contains EtO as an inert ingredient, and there is one application for Federal registration of a State-registered product containing EtO as an active ingredient. EtO is used primarily for sterilization of medical supplies and equipment (see Appendix A for examples) on

which FDA establishes tolerances (53), and as an insecticidal, fungicidal, and bactericidal fumigant on copra, black walnuts, and spices. There are EPA-established tolerances of 50 ppm on these stored food products. In addition, EtO is used to disinfect commercial premises, dental instruments, clothing, laboratory animal bedding, laboratory equipment, and pharmaceutical equipment and materials. A more comprehensive site/pest listing has recently been prepared (83).

In accordance with Section 24(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), three EtO products have been registered in States that have demonstrated that these products are necessary to meet special local needs (Appendix B).

E. Production

Section 7(c) of FIFRA requires manufacturers and formulators to submit to EPA information on the production, sales, and distribution of their pesticide products. According to Sections 7(d) and 10 of FIFRA, this information is confidential and may not be made available to the public. However, a confidential memo summarizing this information (12) has been sent to the Deputy Assistant Administrator for Pesticide Programs.

II. Regulatory History

In 1968 the U.S. Department of Agriculture Pesticide Regulation Division issued cancellation notices for the registrations of EtO for use on dry beans, all grains, almonds, cashews, chestnuts, filberts, hazelnuts, hickory nuts, pecans, walnuts, and peas (PR Notice 68-5). These uses had previously been registered on a "zero tolerance" or "no residue" basis.

In 1969 the Report of the Secretary of Health, Education and Welfare's (HEW) Commission on Pesticides and Their Relationship to Environmental Health [Mrak Report (62)] listed EtO as an epoxide compound having chemical structures known to affect DNA. The report stated, "Any compound having such a structure should be proven to be harmless before humans are exposed to it."

In May 1975 the Food and Drug Administration (FDA) prepared a memorandum (53) which addressed the safety and efficacy of EtO when used as a sterilant and fumigant. Among the recommendations was that the following animal studies be expeditiously undertaken: a teratology study, a mutagenicity study, and a 3-year study for carcinogenicity that would include a limited study of reproductive effects. The Commissioner of Food and Drugs requested that the Associate Commissioner for Science study this recommendation.

In August 1976 the office assigned to review the recommendation suggested that no further studies be initiated at that time by FDA because preliminary tests were underway for five of the six recommended studies at the Carnegie-Mellon Institute of Research. In addition, the National Cancer Institute (NCI) had scheduled carcinogenicity bioassays on EtO and ECH (29).

We have confirmed that on April 27, 1977, the Carnegie-Mellon Institute of Research began a 2-year EtO inhalation study on rats. The protocol indicates that the animals will be examined for oncogenic and cytogenetic effects. To our knowledge, however, neither the teratology nor the reproductive effects study was completed. NCI still has both EtO and ECH tentatively scheduled for bioassays.

In April 1977 an HEW Subcommittee issued the "Report of the Subcommittee on the Benefits and Risks from the Use of Ethylene Oxide for Sterilization" (24). The conclusions were as follows:

> The Subcommittee has concluded that ethylene oxide is an extremely useful chemical which, unfortunately, possesses mutagenic properties. There is little evidence that it is also carcinogenic to experimental animals, although adequate testing has yet to be conducted. Based on the documented mutagenicity of this compound, it is imperative that unnecessary and improper use of ethylene oxide for hospital

> sterilization purposes be prohibited, and that where ethylene oxide can be replaced by another practicable sterilization process, this should be done, providing the alternate process does not possess similar or more serious toxicologic properties. Where the use of ethylene oxide is to be continued, improved techniques of exhausting the gas from the sterilizer, the aerator, and the sterilized items need to be implemented. Gas sterilization should be supervised and monitored so as to prevent all unnecessary exposure to personnel. It is felt that this can be accomplished through improved exhaust, ventilation, and other engineering control techniques. Personnel should be trained in the safe operation of the process. Provided these control measures are instituted (and enforced), the use of ethylene oxide for specific health care applications should carry minimal risk to the health of hospital personnel. The benefits resulting from the use of ethylene oxide are the reduction in the prevalence of coincident infections in patients requiring health care.

On September 30, 1977, the Agency received the "Special Occupational Hazard Review and Control Recommendations for the Use of Ethylene Oxide as a Sterilant in Medical Facilities" (28) that was prepared by HEW's National Institute for Occupational Safety and Health (NIOSH). In the preface of this review, it is stated that this type of review is "...prepared in such a way as to assist in the formulation of regulations." In the summary and conclusions section of the review, it is stated that, "The adequacy of the current U.S. EtO standard [i.e. the time-weighted average of 50 ppm EtO for a workday], which was based on the data available at

the time of promulgation, has not been addressed in this report." The report did recommend that "...exposure to EtO be controlled so that workers are not exposed to a concentration greater than 135 mg/cu m (75 ppm) determined during a 15-minute sampling period..." and that measures be taken to minimize the mutagenic health risk. The report also states that there are plans to develop a criteria document during the 1980 fiscal year which will fully examine the adequacy of the current 50 ppm U.S. EtO standard.

III. Summary of Scientific Evidence in Support of Rebuttable Presumption

A. Mutagenic Effects

40 CFR Section 162.11 (a)(3)(ii)(A) states that "a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s)...induces mutagenic effects, as determined by multitest evidence." Section 162.3 (y) defines mutagenic as "the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations." Section 162.3 (l) defines degradation product as "a substance resulting from the transforma-

tion of a pesticide by physicochemical, or biochemical means."

Evidence in both prokaryotic (e.g. bacterial) and eukaryotic (e.g. animal and higher plant) systems indicates that EtO is a general point (gene) mutagen. This means that EtO can interact with DNA of various species to produce mutations in both reproductive and other body cells. There is also evidence that EtO can induce chromosomal mutations in somatic cells of humans and other mammals. In addition, ECH, an EtO degradation product, has been shown to be a point (gene) mutagen in bacterial systems.

Human exposure to a mutagen has serious implications. The possible adverse effects to people, especially those of reproductive age, are: spontaneous abortions, stillbirths, birth defects in their children, and diseases in the adult life of subsequent generations. Any of these effects could result from exposure of the male and/or female parent to a mutagen. In addition, those exposed can be adversely affected by mutations of the somatic cells.

The Ethylene Oxide Working Group has concluded that EtO and ECH meet this risk criterion and are capable of inducing chromosomal mutations in animals.

1. Ethylene Oxide

a. Point (Gene) Mutations

i. Microorganism Studies

Embree (22) placed EtO-impregnated Tygon tubing on Salmonella typhimurium test strains TA 1535, TA 1537, and TA 1538 on agar plates without microsomal activation. The EtO slowly leached into the plates causing a statistically significant ($p<0.05$) number of histidine revertants (reversion to the wild type at the histidine locus) in strain TA 1535. This indicated that mutation by base-pair substitution had occurred. Tests with strains TA 1537 and TA 1538 were negative. This suggests that EtO does not induce frame-shift mutations.

Rannug et al. (69) dissolved EtO in ethanol and applied the solution to S. typhimurium strain TA 1535 on agar plates without microsomal activation. The concentrations tested were 0.96, 4.77, 9.55, 47.7, and 95.5 mM EtO. A highly significant dose-response relationship for the induction of mutations was observed. These data confirm EtO's ability to induce mutation by base-pair substitution.

In an addendum to Rannug's paper (69), Hussain and Osterman-Golkar (37) reported the genetic risk (potency) of EtO. Using the dose-response curve of the frequency of mutation in Escherchia coli, the authors estimated this risk of EtO to be two mutants per 10^8 survivors per mM x hour.

A Stanford Research Institute study (46) established that there is a dose-response relationship for mutations in S. typhimurium strains TA 1535 and TA 100 exposed to atmospheres with varying concentrations of EtO ranging from 0.01 to 0.1%. These treatments were administered in 9-liter desiccators. There were negative results in strains TA 1537, TA 1538, and TA 98. This study confirmed that EtO induces mutations by base-pair substitution. A rat liver microsomal activation system (induced with Arochlor) was used and did not affect the mutagenic activity. This indicates that EtO is a direct-acting point (gene) mutagen in microbial systems. Microsomal activation provides information on the effect which mammalian metabolism can have on the genetic activity of a compound. The possible effects are the conversion of a promutagen to a mutagen and the conversion of a direct-acting mutagen to nonmutagen.

Kolmark and Westergaard (49) tested a 0.025 M EtO aqueous solution on an adenine-requiring strain of Neurospora

crassa (W.40) in a plate test. The observed frequency of reverse mutations (reversion to the wild type at the adenine locus) increased with the duration of exposure.

Kolmark and Kilbey (48) observed an increased incidence of reverse mutations in the macroconidial strain [K3/17 ad-3A (38701)] of N. crassa which were exposed to 1.5 to 150 mM EtO in culture media. The increase in the frequency of mutation was a function of dose and length of exposure. Kilbey and Kolmark (47) observed the same effects in a similar study.

ii. Plant Studies

Studies of barley, wheat, and rice that were treated with EtO provide convincing evidence that such treatment results in heritable, viable mutants among the segregating generations (17,19,32,40,41,55,73).

iii. Invertebrate Studies

Bird (8), Nakao and Auerbach (63), and Watson (88) injected Drosophila melanogaster males with aqueous solutions of EtO. Following these single doses of EtO at 55 to 175 mM, the males were mated with untreated females. The resulting progeny were examined for recessive lethal mutations

on the X-chromosome (Muller-5 test). The increased incidence of these mutations showed a dose-response relationship.

b. Chromosomal Effects

i. Cytogenetic Studies

In an *in vivo* cytogenetic study, Embree (22) exposed six male Long-Evans rats to 250 ppm EtO in a flow-through chamber for 7 hours per day on 3 consecutive days. Treated rats were sacrificed 24 hours after the last exposure. Several types of chromosomal aberrations were observed in the bone marrow. Incidences of chromatid gaps, isochromatid gaps, chromatid breaks, isochromatid breaks, rearrangements and exchanges, dicentrics, rings, cells with more than one type of aberration per metaphase plate, and abnormal chromosome counts were significantly higher ($p<0.05$) in the exposed animals than they were in the controls.

In a similar experiment Embree (22) exposed groups of five male Long-Evans rats to 10, 25, 50, 250, or 1,000 ppm EtO in air. An additional group of five was exposed to 50 ppm. Treatment involved a single 4-hour exposure. The animals were biopsied 24 hours after treatment. The incidence of micronuclei in polychromatic erythrocytes from bone marrow of treated rats was higher than it was in the controls.

This increase was significant for the two 50 ppm groups (<0.0025*) and for the 250 and 1000 ppm groups ($p<0.05$). A dose-response relationship was demonstrated.

Strekalova (80) administered a single oral dose of 9 mg/kg of EtO in water to two groups of six male rats. The animals were sacrificed after either 24 or 48 hours and bone marrow from the femur was examined for chromosomal rearrangements. The treated rats from both the 24- and 48-hour groups evidenced a higher incidence of chromosomal and chromatid bridges and fragments than did the controls. This increased incidence was significant after 24 hours ($p<0.001$) and after 48 hours ($p<0.002$).

Strekalova et al. (81) continuously exposed a group of 24 male white rats to air containing EtO at 1.98 ± 0.33 ppm for 66 days. The animals were then maintained in uncontaminated air for 4 days before sacrifice. Spinal cord cells were examined and showed an increased incidence of chromosomal rearrangements in the treated rats at both exposure levels as compared to the controls. The statistical significance was not given and the rearrangements were not discussed.

*Assuming totally independent events

Pomenko and Strekalova (26) observed the bone marrow cells of mongrel albino rats which were exposed to EtO by inhalation. Groups of six animals were continuously subjected to 0.55 - 1.65 ppm or 33 ppm EtO for 2, 4, 8, or 30 days. There was evidence of an increase in chromosomal aberrations that was dose and time dependent. As presented, the results do not allow statistical evaluation. The Office of Special Pesticide Reviews sent a memorandum to the Office of International Activities concerning this translation (11).

ii. Dominant-Lethal Assays

Embree (22) exposed 15 male Long-Evans rats to air containing 1000 ppm EtO for 4 hours. After a 24-hour recovery period, each treated male was placed with two virgin females which were replaced each week for 10 weeks. In matings from weeks 1, 2, 3, and 5, the mutagenic index (dead implants/total implants) of the EtO-treated males was significantly higher than that of controls ($p<0.05$).

Strekalova et al. (81) observed male white rats that were continuously exposed to EtO for 66 days. Twenty-four and 14 animals were maintained at levels of 1.98 $\pm$ 0.33 ppm and at 61.5 $\pm$ 11.1 ppm in air, respectively. Immediately following exposure the animals were allowed to mate with

untreated females for 4 days. Mortality of the embryos resulting from mating of males exposed at the higher level was elevated at the $p<0.001$ level of significance, while the lower level of exposure also increased mortality at the $p<0.05$ level of significance.

iii. Human Mutagenic Episode

Ehrenberg (13) studied the lymphocytic effects in seven workers who were transiently exposed to a high concentration of EtO for 2 hours after an industrial accident involving an EtO spill. Since two of the seven workers were hospitalized with lung damage, Ehrenberg (66) estimated the level of exposure to be equivalent to 2 hours of continuous exposure to 1500 ppm. Eighteen months afterwards, peripheral blood lymphocytes were examined for chromosomal aberrations, including chromosomal translocations, gaps, breaks, and aneuploidy. When compared with 10 control subjects with no history of EtO exposure, the incidence of these aberrations was elevated ($p<0.05$).

2. Ethylene Chlorohydrin

a. Point (Gene) Mutations

i. Microorganism Studies

Embree (22) placed a small amount of ECH on agar plates

with S. typhimurium and tested it in the manner previously described. Only the TA 1535 strain, which had an increased incidence of reverse mutations, was significantly affected ($p<0.05$).

Malaveille et al. (56) obtained positive results when they tested ECH at 0.4, 4, and 40 uM/ml on strain TA 1530 in plate tests both with and without microsomal (mouse liver) activation. Metabolic activation enhanced the activity of ECH. There was a positive dose-response relationship. Positive results in this strain of bacteria show that ECH was inducing base-pair substitutional mutations.

Voogd et al. (86) observed a significant ($p<0.05$) increase in the frequency of mutation in Klebsiella pneumoniae which were exposed to ECH in culture media lacking microsomal activation. This test organism is ordinarily dependent on an exogenous source of proline and uracil for growth. These mutants were apparently autotrophic revertants. Results indicate a dose-reponse correlation.

McCann et al. (58) observed reverse mutations at the histidine locus in S. typhimurium strain TA 100, and a weak response with TA 1535 by plate tests both with and without microsomal activation. The incidence of these ECH-induced

revertants in TA 100 was enhanced by metabolic activation. The frequency of mutation increased with the dose in strain TA 100.

Rosenkranz et al. (71,72) obtained a positive response with S. typhimurium strains TA 1530 and TA 1535 after treatment with ECH. This indicated a base-pair substitutional mechanism for the mutagenic action of ECH. A dose-response correlation was demonstrated in strain TA 1530. E. coli (pol $A1^-$) deficient in DNA polymerase also demonstrated a higher degree of inhibition when exposed to ECH than did the pol A+ strain from which they were derived. This indicates that ECH is capable of interacting with DNA.

Rannug et al. (69) observed a significant ($0.001<p<0.01$) increase of S. typhimurium strain TA 1535 mutants in a plate test with 1.0 M ECH. Chloroacetaldehyde, a possible metabolite of ECH, was shown to significantly ($p<0.001$) increase these mutations at 0.5 and 1.5 mM.

Hussain and Osterman-Golkar (37) calculated the genetic risk of chloroacetaldehyde from a dose-response curve of its induction of mutations in E. coli. This risk was defined as 30 mutants per 10^8 survivors per mM x hour.

Elmore et al. (23) reported that chloroacetaldehyde and ECH were mutagenic in a reversion (point mutation) test with S. typhimurium strains TA 1535 and TA 100 and in a DNA repair test with Bacillus subtilis DNA repair-deficient strains. This indicates a base-pair substitutional mode of action. Dose-response curves were generated for these direct-acting mutagens. The effects were highly significant for chloroacetaldehyde.

ii. Animal Cell Study

Huberman et al. (36) detected no induction of 8-azaguanine and ouabain-resistant mutants among Chinese hamster V79 cells which were exposed to ECH. However, a potential ECH metabolite, chloroacetaldehyde, showed positive results.

b. Chromosomal Effects

In a cytogenetic study, Semenova et al. (75) placed albino rats in flow-through inhalation chambers and exposed them to 0.38 $\pm$ 0.073 ppm or 3.2 $\pm$ 0.097 ppm for a period of 4 hours per day for as long as 120 days. Serial sacrifice and examination of bone marrow cells indicated a progressive, statistically significant increase ($p<0.05$) in chromosomal aberrations from the first through sixtieth day. The same effect was observed on the 120th day but it was less significant ($p=0.1$). Following the full regimen of exposure and a

2-week recovery period, there was still an effect (p=0.1).

3. Ethylene Glycol

In a point (gene) mutation study, Embree (22) tested a small amount of EG on S. typhimurium strains TA 1535, TA 1537, and TA 1538 on agar plates without microsomal activation and found no revertants.

B. Reproductive Effects of Ethylene Oxide

40 CFR 162.11 (a)(3)(ii)(B) provides that a rebuttable presumption shall arise if a pesticide "[p]roduces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety." Studies conducted with guinea pigs and rats indicate that EtO can adversely affect the male reproductive organs.

A study (20) in which male mice were exposed to air contaminated with radio-labeled EtO demonstrated residual radioactivity in the testes. In addition, male rats exposed to EtO in the air demonstrated affected germ cells as evidenced in each of two dominant lethal assays (22,81).

Hollingsworth et al. (33) observed atrophic effects on the testes of eight male guinea pigs which were exposed by inhalation to 357 ppm EtO in 123 seven-hour doses during a 176-day study. All animals survived, but appreciable degeneration of the testicular tubules and replacement fibrosis was noted. Hollingsworth also exposed the same number of guinea pigs to 204 ppm EtO in the same manner and observed a slight decrease in the weight of the testes. However, no histopathological effect was noted. In another test, 20 male rats which were exposed to 204 ppm EtO for 122 to 157 seven-hour periods during 176 to 226 days were noted to have small testes and slight degeneration of tubules. There was no evidence that withdrawal from exposure would allow restoration of the testicular structure. The authors also reported that there was no testicular histopathology or gross effect on guinea pigs or rats that were exposed to 113 ppm EtO in air. The exposure regimen consisted of 122 to 157 seven-hour periods during 176 to 226 days. No measure of fertility was taken in any of these tests.

In view of these findings, the Working Group has used 113 ppm as the no-observable-effect level (NEL) in assessing the margin of safety for humans.

In the only available epidemiological study mentioning the effects of EtO on the genital system, Joyner (45) examined 37 workers with an average of 10.7 years of continuous occupational exposure to 5 to 10 ppm EtO in the air. There were no statistically greater incidences of such genital disorders as benign prostatic hypertrophy, acute prostatitis, spermatoceles, or seminomas of the testicle. However, no measure of reproductive capacity was taken.

There appear to be two populations at risk with respect to this potential adverse effect: 1) men who use this pesticide in the operation of EtO sterilization equipment on a routine basis and/or spend most of their time in the immediate area of the operation of this equipment, and 2) men who use EtO as a fumigant on a routine basis and/or often enter storage chambers shortly after such fumigation.

The most applicable level of inhalation exposure which is available for sterilization uses is commonly referred to as "a time-weighted average" (TWA). The most accurate indication of exposure to the EtO sterilization user is a TWA taken by continuously monitoring the breathing zone of the user throughout a typical work day and averaging the results. The Working Group is aware that, in practice, EtO sterilization equipment and conditions are many and varied.

However, the Working Group has only four TWA's on which to base its exposure estimate. Three of the TWA's were provided by the U.S. Army's Environmental Hygiene Agency (27) and represented the "worst case" for individuals operating the machines tested. These TWA's, 16, 8, and 5 ppm, were well below the 50 ppm standard set by the Occupational Safety and Health Administration and currently in force for the workplace. The fourth TWA was supplied to EPA by a pesticide registrant (78). The breathing zone was continuously sampled to reflect actual use conditions. The TWA for this sterilization equipment was shown to be 0.16 ppm. The average of the four TWA's is approximately 7.3 ppm.

Assuming 7.3 ppm to be an approximate indication of the amount of EtO to which men using EtO sterilization equipment are continuously exposed, the Working Group compared this level to the NEL in male rats and guinea pigs (113 ppm).

In order to express these exposure levels as absorbed dose levels, compare these doses, and estimate the margin of safety, the Working Group made certain assumptions: 1) rodents and man receive this dose of EtO primarily by inhalation, 2) the efficiency of uptake of the EtO by this route is the same in man as it is in rodents, and 3) the dose is proportional to the respired volume of EtO-contaminated air.

Once the relationship between exposure levels and absorbed dose levels is empirically established for a laboratory rodent, this relationship can be extrapolated to other laboratory rodents and humans. A series of experiments published by Ehrenberg et al. (20) provides the empirical data to determine the dose-exposure relationship for mice. In these experiments the EtO exposure level and duration of exposure varied. There were a total of seven values of exposure (ppm x hour) and absorbed dose during exposure (u mole/kg). These data were plotted and the slope was used to estimate the dose per unit of exposure times the duration of exposure in mice. The Working Group estimated that exposure to 1 ppm for a period of 1 hour gives mice an absorbed dose of 2.8 u mole/kg. Although part of this dose may have been absorbed dermally, the Working Group assumed that most of the dose was absorbed by inhalation.

Using average body weights and a respiratory rates (4), the Working Group estimated average respiratory intake to be as follows:

Humans (68.5 kg males) doing light work:	25.0 liter/hour/kg
Guinea pigs (466 g):	20.6 liter/hour/kg
Rats (113 g):	38.4 liter/hour/kg
Mice (20 g):	72.1 liter/hour/kg

The Working Group then calculated the average daily doses based on the proportion of respired air of guinea pigs, rats, and men to the respired air of mice. The average daily doses administered to the guinea pigs and rats in the Hollingsworth study at the NEL (113 ppm) were estimated to be 28.2 and 52.6 mg/kg, respectively, whereas the daily dose to men doing light work while breathing air containing 7.3 ppm EtO was estimated to be 2.5 mg/kg. The difference between these estimated NEL doses in guinea pigs and rats and the estimated dose for men does not appear to provide an adequate margin of safety.

The Working Group is not aware of any data which quantify exposure to users of EtO fumigants. Labels of EtO fumigation products typically provide that fumigation be done only by experienced operators and that gas masks be worn prior to entering an area that is known to contain EtO vapors. However, the labels indicate that safe entry following fumigation does not require a gas mask unless there is a noticeable odor.

In the opinion of the Working Group, the warning based on noticeable odor is not sufficient to ensure that exposure to potentially hazardous levels of EtO will not occur. Based on published data (39), the median concentration of EtO which people can detect by smell is 700 ppm; the 95%

confidence interval is 317 to 1540 ppm. The presence of other odorous ingredients in these pesticide products complicates precise utilization of these data. Sexton's review of medical and toxicological literature on EtO (76) also bears on this issue. He stated that, "When highly diluted with air ethylene oxide is only slightly disagreeable and is readily respirable. Prolonged exposure of this type is associated with early olfactory fatigue, and exposure may be prolonged to the point of considerable total absorption of ethylene oxide without warning."

Therefore, entry (e.g., loading and unloading) into the fumigation chambers and vaults between actual fumigation treatments may result in significant inhalation exposure to male fumigators. Although the Working Group is unable to quantify the amount of exposure, it is reasonable to anticipate that such exposure is too high in relation to the no-effect levels in rats and guinea pigs. Accordingly, a rebuttable presumption against registration has arisen against all pesticide products containing EtO.

The Working Group has also determined that dietary intake of stored food products (i.e., spices, copra, and black walnut meats) which have been fumigated with EtO does not appear to result in exposure to levels of EtO that might

affect the gonads. An estimate of EtO ingestion that was based on actual EtO residue data was recently completed (60). Based on this analysis, the Working Group estimated that a 65-kg man would ingest approximately 0.0003 mg/kg/day. The Working Group concluded that there is an adequate margin of safety between the amount of EtO that might be ingested in stored food products and the estimated doses for which the Working Group has calculated that there will be no effect (28.2 and 52.6 mg/kg/day in guinea pigs and rats, respectively).

IV. Other Possible Chronic or Delayed Adverse Effects

EtO and its two principal degradation products, ECH and EG, have been identified in several studies as the cause of a number of other chronic effects. The available information, however, is insufficient to support a rebuttable presumption against EtO. The Working Group is aware that studies currently underway address some of these effects. However, the Working Group is seeking any and all information which might be available to aid the Agency in further assessments of these effects.

A. Oncogenic Effects

The Working Group referred all available data concerning oncogenicity to the Agency's Carcinogen Assessment Group

(CAG) for review. A summary of the findings and conclusions from their report (2) is given below.

1. Ethylene Oxide

There are few published oncogenic studies on EtO, although a 2-year study is now being conducted. The available experiments are reviewed below.

a. Human Epidemiology Study

In a study of 37 operators at a plant producing EtO, Joyner (45) found no increased incidence of tumors in operators exposed to 5 to 10 ppm EtO. Three other operators who were exposed to EtO declined to participate in the study. All subjects were males who were 29 to 56 years old. The mean period of exposure for the group was 40 hours a week for 10.7 years. Operators were exposed to EtO for the following lengths of time: less than 5 years, 3; 5-10 years, 11; 10-15 years, 21; and more than 15 years, 2. This exposure estimate was based on current measurements and the assumption that the exposure had remained essentially the same since the plant process and equipment had been unchanged for 10 years.

Subjects were compared to a control group of 41 drawn from operators who worked in other production units at the

plant and participated in the periodic physical exam program. Control group members had been employed at the plant for an average of 11.7 years. Controls were matched by age only. No attempt was made to analyze the exposure of the control group to other chemicals produced at the plant. There were no clinical signs of toxic effects in this group.

A complete history and physical examination was performed on each member of the study and control group. There was special emphasis on signs suggesting hepatic or renal toxicity. Laboratory tests including chest X-rays, ECG's, hemoglobin tests, and white and red blood counts were done. Medical records for each person were evaluated for complaints in the preceeding 10 years and physicians' diagnoses in the previous 7 years. However, no attempt was made to control for possible biases introduced by variations in medical care or physician diagnoses.

Table 1 summarizes tumors found in the EtO operators and the control group during the 8-year period discussed in the study. Four operators who were exposed to EtO and six control group members had tumors. The health of the operators exposed to EtO was no worse than that of the controls.

Table 1. Incidence of neoplasms among operators in an EtO plant, 1955-1962[1/]

Neoplasm	No. Operators with Neoplasms[2/]	
	Operators Exposed to EtO	Control Operators
Adenocarcinoma (bladder)	1	0
Basal cell carcinoma (skin)	0	2
Seminoma (testicle)	0	1
Lipoma	1	0
Other benign neoplasms	2	3
TOTALS	4	6

1/ Data from Joyner (45).
2/ There were 37 operators who were exposed to EtO and 41 operators in the control group.

It should be noted that the study was designed to evaluate the overall health effects of EtO exposure; tumor incidences were only one aspect of that evaluation. The study group included only operators currently working in the plant. This introduces a possible bias in determining tumor incidence. Because exposed operators who had left the plant were not included, there is no way of knowing whether they developed tumors. Joyner reported that the records of eight former employees were reviewed but does not explain how the eight were selected. Clearly, such a sample can not be considered representative of the exposed population. Indeed, the sample could have systematically omitted those who, because of serious adverse effects from EtO exposure, left the plant.

b. Mouse Study

Van Duuren et al. (84) used 8-week-old female Swiss-Millerton mice to study the effects of dermal exposure to EtO. The authors painted the clipped dorsal skin of 30 mice with approximately 100 mg of a 10% solution of EtO in acetone three times a week during their lifetime. Sixty mice were treated with acetone alone and 60 were untreated. Thirty positive controls were painted with a 2% solution of dibenz(a,h)anthracene (DBA) in acetone.

No tumors or skin irritation were noted on gross examination of the EtO-treated group. The median lifespan was 493 days. It is possible that the EtO could have boiled off the skin of the treated animals and thus would not have remained in contact with the skin to produce an effect.

Carcinomas were detected and confirmed microscopically on 90% (27 of 30) of the DBA-treated group, and were absent from control groups that were untreated or treated with acetone.

c. Rat Study

Walpole et al. (87) tested various alkylating compounds on an unspecified strain of rat. A maximum total dose of 1 g/kg of EtO in arachis oil was administered subcutaneously

to 12 rats for 94 days. The dosing schedule was not reported, nor were the age and sex of the animals. The rats were observed for their lifetime, and none of the 12 rats treated with EtO developed tumors.

In the same test, 8 of 12 rats injected with propane-1,2-epoxide developed sarcomas on the site of injection. These positive controls received a maximum total dose of 150 g/kg over 325 days and were observed for life.

2. Ethylene Chlorohydrin

a. Mouse Studies

Homburger (34) conducted two studies of the oncogenic effects of ECH on mice.

In one study an injection site transfer was designed to shorten the latency period between the injection of the carcinogen and tumor development.

One hundred 7-week-old C57BL/6 male mice were subcutaneously injected in the groin with 1.2 mg ECH (the maximum tolerated dose) in 0.1 ml tricaprylin. The number and schedule of doses were not reported.

Five weeks after the injections, the injection sites were excised, pooled, and minced in 6 ml Ringer's solution. The tissue was divided into 25 equal portions, and each was injected into a mouse of the same age and strain as the primary host.

The same methodology was followed with positive and negative controls, which were treated with dibenzpyrene (25 mg) and tricaprylin (0.1 mg), respectively.

Eighteen weeks after the transfer of injection sites, all animals were sacrificed and gross autopsies were performed. No tumors were detected in the ECH-treated group (24 of 25 survived) or in any of the other five test groups. Tumors were induced in 96% of the positive controls within 17 weeks of the site transfer.

In another study, groups of 50 CF1 female mice and 50 A/He female mice were used to study the potential of ECH to induce lung adenomas.

One group of each strain of mice received a single intravenous injection of 1.2 mg ECH. Groups of 50 A/He and 50 CF1 mice were used as controls. Negative controls received 0.2 cc Ringer's solution. Positive controls received 0.05, 0.1, or 0.5 mg dibenzpyrene.

Another test group of 20 CF1 female mice received seven monthly injections of 1.2 mg ECH. Negative controls received a total of 1.4 ml Ringer's solution. No positive controls were used.

Mortality was low. Mice were sacrificed after 28 weeks. Their lungs were inflated with formaldehyde and inspected under a dissecting microscope for tumors visible on the lung surfaces. Histological sections of some tumors were taken.

The tumor incidence in the two studies is shown in Table 2. There was no significant increase in tumors in the ECH-treated group compared to the controls.

Table 2. Lung tumors in ECH-treated female mice[1/]

Dose	Incidence of Lung Tumors			
	CF1		A/He	
	No.	%	No.	%
Single Intravenous Dose				
1.2 mg ECH	5/46	10.9	10/45	22.2
0.2 cc Ringer's solution	7/48	14.6	7/48	14.6
Seven Intravenous Doses				
1.2 mg ECH	5/18	27.8		
1.4 ml Ringer's solution	2/18	11.1		

1/ Data from Homburger (34).

b. Rat Studies

Mason et al. (57) used 344 four- to six-week-old Fisher rats to test ECH and EG. For each compound, 200 animals were divided into groups of 80, 60, 40, and 20 that contained equal numbers of females and males. Mason subcutaneously injected these animals with ECH in saline twice weekly for 52 weeks. Dose levels of ECH administered were 10.0, 3.0, 1.0, and 0.3 mg/kg, respectively. The maximum tolerated ECH dose determined earlier in the study was 30 mg/kg. There were negative and vehicle (0.25 ml saline) control groups containing 60 rats of each sex.

Mortality in the ECH-treated group was 2% at 12 months and 7.5% at 18 months; this was comparable to control mortality. All animals were sacrificed at 12 or 18 months, as planned, and complete autopsies were performed. No retardation in weight gain occurred during the study. Tumors were grouped by injection site and other sites including pituitary (adenoma), adrenal, blood (leukemia), mammary glands, and uterus. Except for total tumors, frequencies were not tabulated by dose level, but only by sex for the pooled treated group. Tumor incidence for all sites is shown in Table 3.

Table 3. Tumor incidence in ECH-treated Fisher rats[1/]

Compound	Dose, mg/kg	Tumor-Bearing Animals			
		Male		Female	
		No.	%	No.	%
ECH	10.0	1/40	3	7/40	18
	3.0	1/30	3	9/30	30
	1.0	1/20	5	4/20	20
	0.3	0/10	0	1/10	10
Negative Control	0	5/60[2/]	8	9/60[2/]	15
Vehicle control (0.25 ml saline)	0	3/60[2/]	5	9/60[2/]	15

1/ Data from Mason et al. (57).
2/. It was stated in the methods section and other places in the paper that there were 50 males and 50 females in each of the two control groups. However, this table and some others gave the number as 60 per sex for each control group. Percentages expressed in this table are based on groups of 60 rats.

Pituitary tumors occurred in 7 of 100 ECH-treated females (all dose levels) compared to 2 of 120 female controls (p=0.049). This strain of rats frequently has a high incidence of pituitary tumors in untreated controls. Therefore, the slight increase noted in this study may not be related to the treatment. No significant increase in tumors occurred at other sites or at all sites combined. No increase in pituitary tumors was seen in males.

The positive controls were divided into four groups of 20 females and 20 males. The first two groups received single subcutaneous injections of 10.0 and 3.3 mg/kg nickel sulfide, respectively. The other two groups received the same doses of nickel sulfide by a single intramuscular injection in the thigh. Mortality was high: 75% at 12 months and 90% at 18 months. Tumor incidences among the animals in the positive control groups were not given.

Ambrose (5) administered ECH in the diet of 35 young weanling rats in concentrations ranging from 0.01 to 0.24%. One group of five rats that were fed only the regular diet served as controls. Treatment continued for 220 to 403 days. Autopsies and histopathological studies were conducted. No tumors were noted.

3. Ethylene Glycol

a. Mouse Studies

The two Homburger oncogenicity studies (34) which were described above also tested for the oncogenicity of EG.

In the injection site transfer study, the methodology and controls were the same as described above under ECH.

Each mouse was administered 26 mg EG. Fifteen of 26 EG-treated mice survived. (Ten mice in one cage were found dead 8 weeks afer the sites were transferred. The carcasses were too autolyzed for study.) No tumors were reported in the EG-treated group.

In the single and repeated intravenous injection studies, each mouse was administered 26 mg EG per injection. The methodology and control groups were the same as in the ECH intravenous study. Tumor increases are shown in Table 4. There was no significant increase in tumor induction in the EG-treated group as compared to the controls.

Table 4. Lung tumors in female mice administered EG[1/]

Dose	Incidence of Lung Tumors			
	CF1		A/He	
	No.	%	No.	%
Single Intravenous Dose				
26.0 mg EG	5/48	10.4	8/41	19.5
0.2 cc Ringer's solution	7/48	14.6	7/48	14.6
Seven Intravenous Doses				
26.0 mg EG	3/20	15		
1.4 ml Ringer's solution	2/18	11.1		

1/ Data from Homburger (34).

Berenblum and Haran (7) painted 4- to 5-month-old female inbred Swiss mice with EG. Two groups of 20 mice each received single applications of EG and 70 applications of croton oil or paraffin as a secondary treatment. The other two groups of 20 mice received 12 applications of EG before being painted 70 times with croton oil or paraffin. There was a 4-week interval between the primary and secondary treatment. The dosing schedule for the two treatments was not stated. Fifteen mice that were painted with EG 12 times received no secondary treatment. The applications were made on about one square centimeter of skin. The animals were observed for at least 43 weeks. The 15 mice that were not treated with a promoter all survived and had no papillomas. Survival for the four groups receiving secondary treatment ranged from 90 to 100%. No papillomas developed in the mice treated with EG only and one developed in each of the two groups treated with EG and croton oil. None of the mice were administered croton oil alone.

Deringer (16) painted the clipped interscapular area of 2.5- to 3.5-month-old male and female mice with EG twice a week for their lifetime. The dosage was not reported. Half of the 68 mice treated did not have hair. The controls were not treated; 100 had hair and 86 did not. The median survival time for both the treated and control

groups was 22 months. There was no increase in tumor induction in the EG-painted group as compared to the controls.

Reyniers et al. (70) observed tumor induction and toxic effects in a colony of inbred germfree albino mice that were placed on corncob bedding treated with EtO. It was not a controlled experiment. The treated bedding was introduced on December 15, 1961, and removed 150 days later on May 15, 1962. When the bedding was introduced, the colony consisted of 112 adult female, 79 adult male, and 10 suckling mice. The oldest animals of the colony were 605 days old, and four females were pregnant. No tumors were observed among an unspecified number of mice of different ages which were killed or died in 1961. The animals were free of polyoma viruses. However, following maintenance on EtO-treated corncob bedding and gross or microscopic examination, 86% of the surviving females from 300 to 900 days old were found to have tumors (Table 5). The tumors were of a wide variety of types including sarcomas, carcinomas, and lymphomas. They appeared from 153 to 194 days after exposure. The high rate of mortality among the male mice early in the exposure period precluded assessment of tumor formations.

According to the authors, "the only change in colony maintenance was the accidental introduction of corncob

bedding treated with EtO." Because other investigators had previously associated toxic effects with EG residues from bedding treated with EtO, the authors tested for and found EG in the EtO-treated bedding. However, they apparently did not attempt to determine whether other toxic compounds (e.g., EtO and ECH) were also present. Therefore, the data are not sufficient to identify the agent(s) responsible for tumor induction.

Table 5. Tumor incidence in females before and after exposure to ground corncob bedding treated with ethylene oxide[1/]

	Age, days								
	100-200	200-300	300-400	400-500	500-600	600-700	700-800	800-900	Total Mice
Before Exposure									
No. Mice with Tumors	0	0	0	0	0	-	-	-	0
No. Mice	21	17	28	7	10	-	-	-	83
After Exposure									
No. Mice with Tumors	0	0	1	3	11	25	17	5	62
No. Mice	11	2	1	8	13	26	20	5	86

1/ Data from Reyniers et al. (70).

b. Rat Studies

Tests on ECH conducted by Mason et al. (57) and described above were also used to test EG. The same methodology and control groups were used. Four dose groups received injections of 1000, 300, 100, or 30 mg EG/kg. Mortality was 2% after 12 months and 5% after 18 months. The tumor incidence for all sites combined is shown in Table 6. The incidence of tumors in the mice treated with EG was not higher than that of the controls.

Table 6. Tumor incidence in EG-treated Fisher rats[1/]

Compound	Dose, mg/kg	Tumor-Bearing Animals			
		Males		Females	
		No.	%	No.	%
EG	1000	2/40	5	6/40	15
	300	1/30	3	9/30	30
	100	2/20	10	3/20	15
	30	0/10	0	1/10	1
Negative Control	0	5/60	8	9/60	15
Vehicle control (0.25 saline)		3/60	5	9/60	15

1/ Data from Mason et al. (57).

4. Conclusions

CAG has concluded that the information available is insufficient to judge the safety of EtO in regard to oncogenicity. Although most of the tests for oncogenicity have thus far been negative, further study of the possible oncogenicity of EtO is warranted for at least two reasons. First, CAG has concluded that EtO and its degradation product ECH are mutagens. There is a strong correlation between oncogenicity and mutagenicity. Secondly, chemicals which are structurally related to EtO have been reported to be oncogenic (2).

Following review of essentially the same data, the International Agency for Research on Cancer (38) similarly concluded: "Although no carcinogenic effect was observed, the data do not allow an evaluation."

The Ethylene Oxide Working Group concurs with CAG's conclusions and adds the following observations.

a. Lymphatic Leukemia

Brewer et al. (13) presented data from Ehrenberg and Hallstrom that were described above. The occurrence of one case of lymphatic leukemia among the group of 31 occupation-

ally exposed people compared with none in the control group of 26 may have occurred by chance. However, the Working Group requests epidemiological data on this and other types of cancer incidence among people occupationally exposed to EtO.

b. Positive Ames Test

EtO belongs to the class of compounds termed alkylating agents. Alkylating agents which have been shown to be positive mutagens by the Ames test are frequently carcinogens in mammals. Recent data from the Stanford Research Institute (46) demonstrate that EtO was positive in the Ames test and had a positive dose-response relationship. This data has led the Working Group to suspect that EtO may also be an oncogen.

As previously noted, a carcinogen bioassay of EtO is underway. In addition, the New York University Medical Center is completing a long-term carcinogenicity study which includes ECH.

B. Teratogenicity and Fetotoxicity

1. Ethylene Chlorohydrin

a. Avian Study

In 1974, Verrett (85) tested ECH for teratogenic and

fetotoxic effects on chicken embryos by injecting the compound into the egg via the air cell. When the ECH was administered at 50, 25, 12.5, or 5 mg/kg following 96 hours of incubation, the incidence of teratogenicity and fetotoxicity collectively was significant at the $p<0.05$ level for each of these doses compared to vehicle controls. There was a clear dose-response relationship.

b. Mammalian Study

The positive result in chicken embryos prompted a study in mammals which was recently completed by Courtney (15). ECH did not produce fetal malformations in CD-1 mice whether administered in drinking water (10, 25, 50, 100, or 200 mg/kg/day) or by inhalation (50 or 100 mg/kg/day). The 100 mg/kg/day was the maximum tolerated dose for administration by intubation. The Working Group regards the results in mice to be a more reliable test of this possible effect. Therefore, there is no indication that ECH poses human risk as to teratogenicity and fetotoxicity.

2. Ethylene Oxide

The Working Group is not aware of any study on the teratogenicity or fetotoxicity of EtO. Because a large number of EtO sterilization equipment operators are likely

to be women of childbearing age, the Working Group believes that teratogenicity and fetotoxicity testing in mammals should be conducted.

C. Neurotoxic Effects

The following studies suggest that EtO may cause adverse effects on the nervous system. However, more information is needed in order to assess the histopathology of the nervous system of animals exposed to EtO. It is extremely important that the Agency receive all data concerning possible neuropathy among users of EtO.

1. Ethylene Oxide

Joyner (45) examined 37 workers who had been occupationally exposed to 5-10 ppm EtO for an average of 10.7 years. There were no statistically significant increased incidences of the several nervous system diseases observed in the exposed group compared to the control group.

Hollingsworth et al. (33) studied the effects of EtO on various species by exposing the animals to EtO-contaminated air for 7 hours a day, 5 days a week. Rats, rabbits, and a monkey exposed to 357 ppm (0.64 mg/liter) EtO for up to 85 days developed impairment of sensory and motor functions of the lumbar and sacral region and paralysis and muscular

atrophy of the hind limbs. Each of two pairs of monkeys exposed to 357 ppm for 60 days and 140 days, respectively, also exhibited these impairments. In addition, their reflexes were either poor or absent and their sensation of pain in their hind quarters was greatly reduced. All these effects developed late in the exposure regimen and were reversible. The normal cremasteric reflex was elicited, and the test for the extensor reflex of the soles of the hind feet was negative. These signs are consistent with the existence of a peripheral neuropathy. No micropathology was evident. Guinea pigs exposed to 357 ppm EtO for 176 days did not appear to develop neurological impairment.

Two monkeys exposed to 204 ppm EtO for 176-226 days displayed neurological signs qualitatively similar to those just described with the exception that a positive Babinski's sign was elicited. This suggests that there was a disorder of the pyramidal tract in addition to a peripheral neuropathy. At the same level of exposure, rabbits developed slight to extreme paralysis of the rear legs. No impairment of the nervous system was observed in rats and guinea pigs exposed to 204 ppm EtO in the air. None of the species tested exhibited neurological abnormalities at 113 ppm or 49 ppm.

Similar effects have been observed in humans following misuse of EtO. During a less than 1-year period in 1975-76,

there were three EtO sterilizer users hospitilized with neuropathy of the lower limbs. Clinical observations and followup indicated that these effects were reversible (42).

2. Ethylene Chlorohydrin

Kovyazin (50) reported that mongrel male rats exposed to 10 $\pm$ 0.4 mg/m^3 ECH for 4 months developed signs indicating damage to the central nervous system (CNS). "Vegetative" and "microorganic disorders" of the CNS were observed in workers (18.9% of 113) who had 2 to 7 years of exposure to 4 to 10 mg/m^3 ECH.

D. Sensitivity and Hypersensitivity

EtO sterilization residues, collectively, may be a serious problem to hypersensitive people [see anaphylactic reaction reported by Poothullil et al. (67) and described below]. Because of the nature of this specific exposure, the Working Group is referring this finding to FDA.

Three of the eight people tested showed sensitivity (77) with almost the same latency period. Data pertaining to ECH and EG that are presented in this part indicate that these degradation products do not independently elicit this delayed toxic effect.

1. Ethylene Oxide

Woodard et al. (90) administered EtO dermally (0.5 ml of 1%) or intracutaneously (0.5 ml of 0.1%) to separate groups of 10 male guinea pigs three times a week for 3 weeks. Results were negative.

Sexton et al. (77) exposed the forearms of eight human subjects to aqueous solutions of EtO. Following a varyihg regimen of topical dermal exposure to between 1 and 100% EtO for between 18 seconds and 60 minutes, three cases of sensitivity were observed (two after 19 days and one after 20 days). This was evidenced by pruritus and erythema with slight edema.

Thiess (82) applied 1% EtO to the skin of 30 production plant workers who had an average of 10.4 years of occupational exposure. There was no evidence of sensitization.

Royce et al. (74) observed that occupational dermatitis was caused by EtO. The Working Group requests information as to the frequency of this condition among users of EtO.

2. Ethylene Chlorohydrin

Lawrence et al. (54) intradermally injected groups of five Hartley strain guinea pigs (0.1 ml of a 10% ECH

solution or 0.1 ml of a 5% ECH solution) with Freund's complete adjuvant. After 1 week, a 10% ECH solution was applied topically. After an additional 2 weeks, ECH was applied topically and an occluding bandage was attached for 1 day. Results were negative.

Woodard et al. (90) administered ECH dermally (0.5 ml of a 1% solution) or intracutaneously (0.5 ml of a 0.1% solution) to separate groups of 10 male guinea pigs three times a week for 3 weeks. Results were negative.

3. Ethylene Glycol

Woodard et al. (90) also administered EG as described above and obtained negative results.

4. EtO Sterilization Residues

Poothullil et al. (67) reported an anaphylactic reaction in a patient which they attributed to EtO residues from a kidney machine sterilized with EtO. The Working Group is referring this information to FDA.

E. Reproductive Effects of Ethylene Glycol

The information summarized in this part suggests a possible link between exposure to EG and decreased fertility

in mice. However, the levels administered were either extremely high or lacked quantification. The Working Group noted the dramatic change in fertility of the mouse colony as well as the lack of experimental design in Reyniers' study.

Elis et al. (21) administered EG orally (0.4 or 0.1% of the parenteral LD_{50}) to mice for 18 days. When compared to negative controls, both groups showed a marked decrease in the number of newborns per exposed female.

Reyniers et al. (70) observed inbred germ-free albino mice that were accidentally exposed to EtO-treated corncob bedding.* They noted that the colony failed to reproduce despite increased matings. This trend was established prior to the incidence of a high level of mortality among males which developed approximately 4.5 months from the beginning of maintenance on the treated bedding. The population included 112 females and 79 males with a demonstrated history of successful matings.

Blood (10) administered 0.2 and 0.5% EG in diets of two male and one female rhesus monkeys, respectively, for 3 years. There were no histopathologic effects in the testes or ovaries.

*These observations are listed under EG because it was present in the bedding material. The levels at which EG was present were not indicated and the bedding was not analyzed for EtO or ECH.

F. Hematological Effects

Available data indicate that EtO, ECH, and EG may cause certain effects in blood.

1. Ethylene Oxide

Ehrenberg and Hallstrom (13) examined 31 people occupationally exposed to 1 ppm EtO in air (67) for an average of 15 years. Compared with a control group of 26, the lymphocyte counts were significantly elevated at the $0.05>p>0.001$ level. There were also three cases of anisocytosis and one case of lymphatic leukemia in the exposed group and none in the controls. This latter effect is more fully discussed in the section on oncogenicity.

Short-term EtO exposure to rats via intraperitoneal injection or inhalation (13) showed the opposite effect: significantly decreased lymphocyte counts. This result followed administration of 50 mg EtO/per kg of body weight in a single dose and 3 hours of exposure to 850 mg EtO per cubic meter of air, respectively.

Hollingsworth et al. (33) observed lymphocytosis in humans after excessive acute exposure to EtO vapor.

Joyner (45) reported a considerable elevation in

white blood cell counts in people exposed to EtO for an average of 10.7 years. After assuming that there is a standard deviation of 1800 white blood cells per cubic millimeter or a coeficient of variation of 30%, Ehrenberg (20) described Joyner's averages as highly significant. However, Union Carbide has now submitted the raw data which indicate the mean values were in arithmetical error and that there was no effect (43).

2. Ethylene Chlorohydrin

Woodard (90) observed an increased leucocyte count in rats after they were subcutaneously injected with 3 to 27 mg ECH/kg for 30 days.

Lawrence et al. (54) observed a significant increase in rat lymphocytes after the animals were intraperitoneally injected with 12.8 mg ECH/kg three times a week for 3 months.

Oser et al. (65) administered 30, 45, or 67.5 mg ECH/kg body weight/day to weanling albino rats (FDRL strain) for 42 and 90 days. Total and differential leukocyte counts were not affected in any group. This blood parameter was also unaffected in pure-bred beagle dogs maintained for 90 days on 600, 900, or 1350 ppm ECH in the diet. In

addition, monkeys (Hacaca mulatta) administered 30, 45, or 62.5 mg ECH per kg body weight per day showed considerable hematclogical variation that was within the normal range.

3. Ethylene Glycol

Allen (3) reported hemorrhagic diathesis in several strains of male mice after they were maintained for 6 months on pine shavings sterilized with EtO. Reyniers et al. (70) also noted hemorrhaging in male mice maintained on EtO-treated corncob bedding.

Kozlenchkov (51) reported leukocytosis in all 48 observed humans who ingested large quantities of EG in a short period of time.

Woodard (90) reported an elevated leukocyte count in rats and increased hematopoiesis in dogs that were subcutaneously injected with from 50 to 450 mg EG/kg for 30 days.

Moriarty et al. (61) noted highly elevated white blood cell counts in humans that had accidently ingested EG.

Appendix A

SPECIFIC CLASSES OF ITEMS STERILIZED WITH ETO WITHIN HOSPITALS OR HEALTH CARE FACILITIES

Anesthesia equipment (masks, bags, tubing, and breathing circuits)

Camera, photographic equipment, lenses, and lamps

Catheters

Diagnostic equipment (x-ray cassettes, blood pressure cuffs, and stethoscopes)

Fiberscope (including broncho-, duodeno-, gastrointestinal-, and laparoscopes)

Implantable prosthetic devices

Laboratory equipment (microscope, endotracheal tube, elastic bandage, hemodialysis coil, venoclysis set, thermometers, PVC oxygen tents, incubators, resuscitation equipment, foam and floatation pads, sigmoidscope specula, epidural cannula, tracheostomy tube, gun rubber mouth prop and dental dam, various syringes including ear)

Respiratory therapy equipment (nebulizer bacteria filters, respirator tubing, spirometer, mask, heart-lung oxygenator machines, humidifier, electronic nebulizer)

Surgical eqiupment (skin scribe pen, nerve locater/stimulator, mercury-filled equipment, electronic defibrillator equipment, cautery and electrosurgical equipment, cryoextractor, air instrument hand pieces and accessories, air supply hose, eye knives)

Surgical supplies (examination glove and finger cots, oral adhesive bandage, gelfoam, endospiral tube, tracheostomy tube, nasal airway tube, tape, sutures (catgut, silk, cotton, and nylon) ampules, vials, and stoppers/caps/ closures)

Telescopic Instruments (broncho- and cystoscopes, electrotomes, and endo-, ophthalmo-, and proctoscopes)

Transducers (pressure, blood flow, and associated cable)

Tubing (natural rubber, polyethylene, polyvinylchloride, latex rubber)

Miscellaneous (dilators, electric cords, hair clippers, pumps, motors, and items from isolation rooms, such as books, toys, blankets, furniture, phones, and TV sets)

Source: Department of Health, Education, and Welfare

Appendix B
Section 24(c) Registrations of Products Containing Ethylene Oxide

1) NJ-770003 (EPA SLN No.)
registered to: New Jersey Department of Agriculture

treatment: bee equipment/bee diseases

issued: March 21, 1977

product: Carboxide (10% Ethylene Oxide)
EPA Reg. No. 10330-6

2) WV-770004 (EPA SLN No.)
registered to: West Virginia Department of Agriculture

treatment: bee equipment/foulbrood disease

issued: July 13, 1977

product: Oxicarb
(No EPA Reg. No. - new product)

3) VA-760014 (EPA SLN No.)
registered to: Virginia Department of Agriculture and Commerce

treatment: For control of Bacillus larvae or other pests of honeybees

issued: December 10, 1976

product: Bee Gas Sterilant Mix
(No EPA Reg. No. - new product)

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